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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT		ATTY. DOCKET NO.
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EXAMINER	
SCHWADRON, R	
ART UNIT	**PAPER NUMBER**
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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) ~~1-153~~ 1-153 is/are pending in the application.
Of the above, claim(s) 18-21, 36-153 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 1-17, 22-35 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☒ The oath or declaration is objected to by the Examiner. SEE OFFICE ACTION

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

15. Applicant's election with traverse of Group I, claims 1-17,22-35 in Paper No. 6 is acknowledged. The traversal is on the ground(s) that are stated in said paper. This is not found persuasive because of the following reasons. Regarding applicants comments about claim 150, said claim is not related to the invention of group II because it is drawn to CD8+ cells, not CD4+ cells. Regarding applicants comments about Groups II and III, and claims 43 and 150, claims 43 and 150 are drawn to product claims wherein the method wherein said product is made carries no patentable weight. Cells identical to those recited in claim 43 can be made by methods other than recited in claim 36. For example, the virally purged cells recited in claim 43 can be made by a process wherein HIV+ cells are eliminated before the CD4+ cells are isolated. Therefore, the cells of claim 43 can be made by a process that is materially different from that recited in claim 36. In addition, the method of claim 1 is not used to produce the cells of claim 43 (eg. claim 1 is not drawn to a method of making virally purged cells). Regarding claims 1 and 150, claim 150 is drawn to a product claim wherein the method wherein said product is made carries no patentable weight. Cells identical to those recited in claim 150 can be made by methods other than recited in claim 1. For example, the cells can be made by expansion in media containing IL-2. Regarding applicants comments about claim 150 and group II, claim 150 is not drawn to virally purged CD4 + cells and is not made by the invention of group II. Furthermore, it is still unclear as to why there is any relation between the invention of group I and that of group II. Inventions I and II are different methods. These inventions require different ingredients and process steps to achieve different goals. Invention I is a method of making immune cells, while invention II is a method of making virally purged CD4+ cells. These methods use different process steps and ingredients to achieve different goals. Therefore they are novel and unobvious in view of each other and are patentably distinct. The requirement is still deemed proper and is therefore made FINAL.

16. Claims 18-21,36-153 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions, the requirement having been traversed in Paper No. 6.

17. Claims 1-17,22-35 are under consideration.

18. Applicants need to list the serial number to which priority is desired under 35 U.S.C. 119(e) (eg. 60/044693) in the first sentence, first page of the specification. Applicants need to list the application number of the PCT to which priority under U.S.C. 120 is desired in the first paragraph, first page of the specification. Applicants need to update the status of all US applications disclosed in the specification (eg. 08/506173 is now US Patent 5,627,070).

19. The oath or declaration is defective. A new oath or declaration in compliance with 37 C.F.R. § 1.67(a) identifying this application by its Serial Number and filing date is required. See M.P.E.P. §§ 602.01 and 602.02.

The oath or declaration is defective because:

It does not recite the serial number of the provisional application to which priority under U.S.C. 119(e) (eg. 60/044693) is claimed and it does not list the application number of the PCT to which priority under U.S.C. 120 is desired.

20. Claim 1-17,22-35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification is not enabling for the claimed invention wherein clinically relevant numbers greater than 10^{10} cells are generated or wherein 10^{10} cells are generated by treatment other than antiCD3 antibody and antiCD28 antibody or antiCD3 antibody in combination with anti CD28 antibody and antiCD5 antibody. The specification discloses that "clinically relevant" cell expansion can encompass methods wherein greater than 10^{10} cells are produced. Claims 14,15,34,35 also read on methods wherein greater than 10^{10} cells are produced. However, there is no disclosure in the specification of actual evidence of any method wherein greater than 10^{10} cells are actually produced. There is also no disclosure in the specification that numbers of cells in the 10^{10} or 10^{9} range can be produced by any method except in methods wherein T cells/T cell subsets are treated with antiCD3 antibody and antiCD28 antibody or antiCD3 antibody in combination with anti CD28 antibody and antiCD5 antibody. There is no evidence disclosed in the specification that treatment with a single antibody will yield clinically relevant numbers of T cells or that treatment with antibody combinations other than antiCD3 antibody and antiCD28

antibody or antiCD3 antibody in combination with anti CD28 antibody and antiCD5 antibody can be used to yield clinically relevant numbers of T cells. In fact, regarding the claimed method as it reads on method which use one activating protein, the art recognizes that at least two signals (eg. treatment with two T cell activating/stimulating agents) are necessary to achieve T cell stimulation/growth (see June et al. WO 95/33823, page 5, lines 21-28). The art also recognizes that T cell stimulation of the TCR/CD3 or CD2 molecule in addition to stimulation via other costimulatory pathways is required to achieve effective T cell proliferation. The specification only discloses evidence indicating that methods wherein T cells/T cell subsets are treated with antiCD3 antibody and antiCD28 antibody or antiCD3 antibody in combination with anti CD28 antibody and antiCD5 antibody can be used to achieve clinically relevant numbers of T cells (eg. 10^{10}). The enablement provided in the specification is not commensurate with the scope of the disclosure of the specification.

21. Claim 1-7,11,13-17,22-25,31,33-35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification is not enabling for the claimed method wherein immune cells per se or regulatory immune cells per se are generated. The specification discloses the claimed methods as methods for generating T cells/T cell subsets. However, immune cells encompasses nonT cells such as dendritic cells, macrophages, NK cells, etc. There is no evidence of record that such cells can be generated using the claimed method. For example, macrophages and dendritic cells are not CD3 or CD2 positive, and therefore said cells could not be grown using the method disclosed in the specification which requires use of a CD3 or CD2 stimulating agent. There is no guidance in the specification as how the claimed method could be used for the growth of dendritic cells, macrophages or other immune cells that are not of the T cell lineage. Therefore, the specification is not enabling for the instant invention.

22. Claims 1-17,22-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2,17,22 are indefinite in the recitation of "regulatory immune cells" because it is unclear what this means or encompasses. The specification on page 19 discloses that "a regulatory immune cell is any mononuclear cell with a defined cytokine production profile in which such cytokine profile does not directly mediate an effector function" and that said cell "has the ability to control or direct an immune response, but does not act as an effector cell in the response". However, it is unclear what this means or encompasses. While the specification discloses that Th1 or Th2 are "regulatory immune cells", the art recognizes that said cells are effector cells with regards to the pathogenesis of a variety of different autoimmune diseases (see Liblau et al., pages 34-38). For example, Liblau et al. teach that Th1 cells are involved in the pathogenesis of IDDM wherein said cells bind islet antigens via TCR mediated antigen specific recognition of said islet antigens (see page 35, first column penultimate paragraph). Liblau et al. teach that the lymphokines secreted by said cells are involved in the pathogenesis of IDDM. Thus, according to the definition in the specification Th1, Th2 or Th3 are not "regulatory immune cells" because they function as effector cells and the cytokines they produce also function in a variety of different effector mechanisms. It is unclear as to what cell population is encompassed by this term and it is unclear what the aforementioned definition actually means. Claims 1 and 22 are indefinite in the recitation of "clinically relevant" because it is unclear what this means or encompasses. The specification discloses that " clinically relevant" in the context of the claimed method means methods for producing typically greater than 10^9 or 10^{10} cells, but does not specifically define what clinically relevant numbers of cells means in the context of the claimed method. For example, it is unclear whether a method which produced 10^8 cells would qualify as a method for producing clinically relevant numbers of cells, because it is unclear as to what number of cells is the lowest number of cells that constitutes "clinically relevant" in the context recited in the claim. Claim 23 is indefinite in that "prior to infusion" lacks antecedent basis in claim 23. Claim 23 is also indefinite in the recitation of "prior to infusion" because it is unclear what this means or encompasses in the context recited in the claim. Claim 27 is indefinite in the recitation of "Th1-like or Th2-like" because it is unclear what these terms mean or encompass. Claim 30 is indefinite in the recitation of "effector cells" because this term lacks antecedent basis in claim 29.

23. Regarding priority for the claimed inventions with regards to the application of prior art, the claimed inventions are not disclosed in parent application provisional application 60/044693

(the application formerly known as 08/506668), and therefore priority with regards to the application of prior art is taken as the filing date of PCT WO 97/052349 to which applicant claims priority. There is no disclosure in 60/044693 of the method of claim 1 for generating "immune cells" per se (60/044693 refers to methods of generating autologous immune cells). There is no disclosure in 60/044693 of the method of claim 1 using the step of "collecting material comprising bodily fluid or tissue containing mononuclear cells from a mammal.". There is no disclosure in 60/044693 of the method of claim 1 using "one or more activating proteins" or wherein said activating proteins are " specific for cell surface proteins present on cells". There is no disclosure in 60/044693 of the method of claim 1 wherein "cells expand to clinically relevant numbers". There is no disclosure in 60/044693 of the methods of claims 2,3,8-12,14,16,17. There is no disclosure in 60/044693 of the method of claim 22 or claims 23-35.

24. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

25. Claims 1,3-7,11,12,14-17,22-25,31,32,34,35 are rejected under 35 U.S.C. 102(b) as being anticipated by June et al. (WO 94/29436).

June et al. teach the method of claim 1, wherein unfractionated T cells or CD4+ or CD8+ cells are expanded to clinically relevant numbers by treatment with antiCD3 antibody followed by antiCD28 or antiCTLA4 antibody (see abstract, pages 4-9,13, claims 1-28,30-37). June et al. teach that prior to treatment said cells can be treated with antigen to induce ex vivo differentiation of said cells into antigen specific effector cells (see page 9, first complete paragraph) and that said cells can be purified (see pages 29 and 300). June et al. teach that the claimed method can be used to produce "regulatory cells" such as CD4+ cells (see page 6). Said CD4+ cells have a defined cytokine production profile, wherein said cytokine profile does not directly mediate an effector function (eg. said cells produce IL-4 which can cause Th2 differentiation). Said CD4+ cells are treated to alter their cytokine profile prior to production in that they are separated from

CD8+ cells (see claim 30).

26. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

27. Claims 1,3-7,11-17,22-25,31-35 are rejected under 35 U.S.C. § 103 as being unpatentable over June et al. (WO 94/29436) in view of Cracauer et al. (US Patent 4,804,628).

The claims are drawn to methods for generating immune/regulatory cells using a hollow fiber bioreactor. June et al. teach the method of claim 1, wherein unfractionated T cells or CD4+ or CD8+ cells are expanded to clinically relevant numbers by treatment with antiCD3 antibody followed by antiCD28 or antiCTLA4 antibody (see abstract, pages 4-9,13, claims 1-28,30-37). June et al. teach that prior to treatment said cells can be treated with antigen to induce ex vivo differentiation of said cells into antigen specific effector cells (see page 9, first complete paragraph) and that said cells can be purified (see pages 29 and 300). June et al. teach that the claimed method can be used to produce "regulatory cells" such as CD4+ cells (see page 6). Said CD4+ cells have a defined cytokine production profile, wherein said cytokine profile does not directly mediate an effector function (eg. said cells produce IL-4 which can cause Th2 differentiation). Said CD4+ cells are treated to alter their cytokine profile prior to production in that they are separated from CD8+ cells (see claim 30). June et al. do not teach the use of a hollow fiber bioreactor in said method. Cracauer et al. teach hollow fiber bioreactors and that the use of such hollow fiber bioreactors for efficiently growing larger numbers of cells in vitro (see columns 1-3). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because June et al. teach the claimed method except for the use of a hollow fiber bioreactor and Cracauer et al. teach hollow fiber bioreactors and that the use of such hollow fiber bioreactors for efficiently growing larger numbers of cells in vitro. One of ordinary skill in the art would have been motivated to do the aforementioned because Cracauer et al. teach that "hollow fiber culture devices have been proven to be ideal for the maintenance of many types of cells at high densities in culture."(column 1).

28. Claims 1-12,14-17,22-32,34,35 are rejected under 35 U.S.C. § 103 as being unpatentable June et al. (WO 94/29436) in view of Garra et al. and prior art disclosed in the specification on page 29 (Hsieh et al., Paliard et al., and Sedar et al.)

The claims are drawn to methods for generating Th1 and Th2 cells. For the purposes of this rejection, Th1 and Th2 will be considered as "regulatory immune cells" because they are defined as such in the specification. June et al. teach the method of claim 1, wherein unfractionated T cells or CD4+ or CD8+ cells are expanded to clinically relevant numbers by treatment with antiCD3 antibody followed by antiCD28 or antiCTLA4 antibody (see abstract, pages 4-9,13, claims 1-28,30-37). June et al. teach that prior to treatment said cells can be treated with antigen to induce ex vivo differentiation of said cells into antigen specific effector cells (see page 9, first complete paragraph) and that said cells can be purified (see pages 29 and 300). June et al. do not teach the claimed method wherein it is used to produce Th1 or Th2 cells. O'Gara et al. teach CD4+ Th1 and Th2 cells (see entire document).O'Gara et al. teach that said cells produce particular types of lymphokines/cytokines (see Figure 1). June et al. teach that their method can be used to expand T cells including CD4+ cells (see claims 1-26). The specification discloses on page 16 that the art recognized that IL-4 treatment of T cells gives rise to Th2 cells and that the presence of interferon-gamma leads to the formation of Th1 (see Hsieh et al., Paliard et al., and Sedar et al.). A routineer would have used Th1 or Th2 cells prepared by said method in the method taught by June et al. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because June et al. teach the method of claim 1, wherein unfractionated T cells or CD4+ or CD8+ cells are expanded to clinically relevant numbers by treatment with antiCD3 antibody followed by antiCD28 or antiCTLA4 antibody, O'Gara et al. teach CD4+ Th1 and Th2 cells, while the art recognized that IL-4 treatment of T cells gives rise to Th2 cells and that the presence of interferon-gamma leads to the formation of Th1 (see Hsieh et al., Paliard et al.,and Sedar et al.). One of ordinary skill in the art would have motivated to do the aforementioned because June et al. teach that their method can be used to expand CD4+ cells and Th1 and Th2 are CD4+ cells. In addition, June et al. teach that their method can be used to expand T cells as a source of T cell cytokines (see page 2, last sentence). O'Gara et al. teach that Th1 and Th2 produce different types of lymphokines/cytokines and therefore by producing Th1 or Th2 cells one could have produced a desired lymphokine or cytokine produced by said cell. A routineer would have used anti-IL4

or anti-gamma interferon antibody in said method to neutralize the unwanted potential cytokine that would interfere with the development of Th1 or Th2 depending on which cell population was desired. If a mixed T cell population was treated with interferon gamma to produce Th1, the addition of antiIL-4 antibody would neutralize endogenous Il-4 produced by the cultured T cells which could lead to Th2 formation.

28. No claim is allowed.

29. Papers related to this application may be submitted to Group 180 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Papers should be faxed to Group 180 at (703) 305-3014.

30. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Ron Schwadron whose telephone number is (703) 308-4680. The examiner can normally be reached Tuesday through Friday from 8:30 to 6:00. The examiner can also be reached on alternative Mondays. A message may be left on the examiners voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ms. Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 180 receptionist whose telephone number is (703) 308-0196.

RONALD B. SCHWADRON
PRIMARY EXAMINER
GROUP 1800

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Primary Examiner
Art Unit 1816
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